Functional and computed tomographic evolution and survival of restrictive allograft syndrome after lung transplantation

Stijn E Verleden[1], Pim A de Jong[2], David Ruttens[1], Elly Vandermeulen[1], Dirk E Van Raemdonck[1], Johny Verschakelen[3], Bart M Vanaudenaerde[1], Geert M Verleden[1], Robin Vos[1]

[1]Leuven Lung Transplant Unit, KU Leuven and UZ Gasthuisberg, Leuven, Belgium

[2]Department of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands

[3] Department of Radiology, UZ Gasthuisberg, Leuven, Belgium

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Address for correspondence: Dr Stijn Verleden
K U Leuven
Lung Transplantation Unit
49 Herestraat, B-3000 Leuven, Belgium
Tel: + 32 16 330194 Fax: + 32 16 330806
E-mail:stijn.verleden@med.kuleuven.be

Abstract

Background: Restrictive Allograft Syndrome (RAS) has been recently defined as a novel phenotype of chronic lung allograft dysfunction (CLAD) after lung transplantation. The goal was to describe CT changes of RAS patients and to correlate this with spirometry and survival.

Methods: All 24 established RAS patients in our center were retrospectively included. CT scans in the pre-CLAD, CLAD, post-CLAD and late-CLAD stadium were systematically evaluated by a blinded observer using a semi-quantitative scoring system. Changes in CT patterns were correlated with spirometry and survival.

Results: The most prominent CT features at diagnosis of CLAD compared to preCLAD were appearance of central (p=0.020) and peripheral ground glass opacities (p=0.052), as well as septal and non septal lines (p=0.020). Survival after diagnosis of CLAD was only associated with the absolute value of Forced Vital Capacity (FVC) at diagnosis (R=0.46 and p=0.021), but not with any CT alterations. Evolution of CT abnormalities after diagnosis of CLAD, included significant increases in (traction) bronchiectasis (p<0.0001), central (p=0.051) and peripheral (p=0.0002) consolidation, architectural deformation (p=0.0002), volume loss (p=0.0004) and hilus retraction (p=0.0036). The absolute FVC decrease post CLAD diagnosis correlated with CT alterations.

Conclusion: In the early stages of RAS, central and peripheral ground glass opacities are the most prominent feature on CT, while in later stages bronchiectasis, traction, central and peripheral consolidation, architectural deformation, volume loss and hilus retraction are more pronounced. CT changes, however, could not predict survival, whereas the FVC at diagnosis of CLAD seems to be the best predictor of survival.

Introduction

Lung transplantation is the ultimate treatment for patients with end-stage pulmonary disorders. Survival remains hampered by chronic rejection of which the clinical correlate is Bronchiolitis Obliterans Syndrome (BOS) with 50% of patients suffering from BOS 5 years after transplantation (1). For over 10 years BOS has been defined as a persistent, obstructive decline in forced expiratory volume in 1 second (FEV_1) in the absence of confounding factors (2). However, nowadays the term chronic lung allograft dysfunction (CLAD) seems more appropriate as it became clear that there are different phenotypes of chronic rejection. First, it was observed that in 35% of so-called BOS patients, azithromycin could improve the FEV_1 with ≥10%, an entity called neutrophilic reversible allograft dysfunction (3). In the broncho-alveolar lavage, these patients display high neutrophil (>15%) counts and on computed tomography (CT), these patients show more centrilobular abnormalities and signs of tree-in-bud, which resolves after treatment (4). Subsequently, attention has shifted to the azithromycin non-responsive CLAD patients. On the one hand, there is a strictly obstructive phenotype with air trapping on expiratory CT and small airway occlusions at pathological examination (obliterative/constrictive bronchiolitis). This pattern is seen in approximately 45% of all CLAD and 70% of all irreversible CLAD patients and is consistent with the definition of BOS. On the other hand a new phenotype has been defined based on a restrictive pulmonary physiology. The entity is defined by using a decline in total lung capacity (TLC) of at least 10% (5) or a progressive decrease in FEV_1 and/or FVC with an increasing or stable FEV_1/FVC ratio (6). This Restrictive Allograft Syndrome (RAS) accounts for approximately 30% of all patients suffering from irreversible CLAD and 20% of all CLAD patients (5,6). Clinically, RAS patients have a median survival of 8 months (versus 35 months for BOS patients) (6). The current study aimed to describe functional and radiological changes in patients, diagnosed with CLAD, who all fulfilled the RAS criteria.

Material and methods

Patient characteristics

Patients who underwent double lung or heart lung transplantation between 2001 and 2012 were retrospectively recruited. All patients provided written informed consent before transplantation. CLAD was defined as a persistent FEV_1decline ≥20% compared to the mean of the 2 best post-operative values. Subsequently, irreversible CLAD was defined as patients without an improvement in FEV_1 after azithromycin therapy. Within the CLAD patient group, RAS was diagnosed in case of restrictive pulmonary function, based upon a decrease in TLC with at least 10%, when available or a FEV_1/FVC ratio >0.70 (with declining FEV_1 and FVC) when TLC is not available. For the purpose of the present study the CT at clinical diagnosis of CLAD was used as a reference scan (CLAD-CT). Pre-CLAD CT was the first CT preceding diagnosis of CLAD. Likewise the first post-CLAD CT (3 months to 1 year after diagnosis of CLAD) and the last available CT scans during follow-up were scored. We used the term CLAD as not all patients immediately develop the typical restrictive pulmonary function defect and we aimed to describe the radiological changes starting from the moment that the FEV_1 consistently remained under 20% of the best post-operative values. Pathology reports were available when patients underwent re-transplantation, open lung biopsy or autopsy and the typical findings were previously described by Ofek et al. and include extensive alveolar fibrosis, septal thickening but also obliterative bronchiolitis (7).

CT protocol

CT examinations were performed on a Siemens Somatom Sensation 16 or 64, a Siemens Definition Flash (Siemens AG, Erlangen Germany) or a Philips Brilliance 64 (Philips Medical Systems, Best, The Netherlands) without intravascular contrast media. One volumetric CT data set of the entire thorax was obtained in suspended deep inspiration in the supine position using 120kV and 140mAs and reconstructed as follows: 1/0.5mm axial, 5/5mm axial and 3/3mm coronal displayed in lung and

mediastinal window-centre settings. Another CT dataset was also obtained after breath-hold instruction at end- expiration with the patient supine but in a sequential mode with collimation 2x1mm and table feed of 30mm using 120kV and 150mAs. Reconstructions of 1mm slice thickness were calculated and displayed in lung window-centre settings.

CT scoring

All the CT data sets were scored using semi-quantitatively scores based on previous descriptions (4,8). On inspiratory CT, the severity and extent of bronchus dilatation (and presence of traction) in the central and peripheral lung were scored, as was the extent of mucous plugging in large airways, extent of centrilobular nodules including tree-in-bud, extent and severity of airway wall thickening, extent of consolidation, extent of ground glass opacities, severity of architectural distortion, volume loss, displacement of the hilum, septal thickening and (sub)pleural thickening. The presence of an apicobasal gradient (apical dominant disease) was recorded. The extent of air trapping was scored on expiratory CT. In general, abnormalities were defined according to the Fleischner Society nomenclature (9). Bronchus dilatation was defined as a bronchus lumen diameter greater than the accompanying pulmonary artery outer diameter, lack of tapering of the bronchus or bronchi visible in the outer centimeter of the lung. Airway wall thickening was defined as a wall thickness to artery diameter ratio >0.2, this was assessed subjectively. Each abnormality was scored in five lung lobes, and per lobe the extent involved with the abnormality was estimated as less than one-third, between one-third and two-thirds, and more than two-thirds of the lobar volume or as mild, moderate or severe. To assess severity, this number was turned into percentages of the lung that are affected. Lung periphery was defined as the outer one-third of the lung. CT data sets were scored by one board certified chest radiologist (PDJ) with over 10 years of experience in reading chest CT scans for whom the reproducibility for most items has previously been described (8). CT examinations were scored blinded to the time-point of diagnosis. Both coronal and axial images were used for scoring.

Statistics

All values displayed are mean±SEM. CT scorings before and at diagnosis of CLAD were compared using Wilcoxon matched pairs test. Evolution of CT throughout time (CT at diagnosis of CLAD, 3 to 12 months after diagnosis and last available CT) were compared using a friedman test. Survival analysis was performed with Kaplan-Meier curve comparison. Correlation was performed using Spearman rank test. Spirometric values at the moment of the HRCT scan were used for this analysis. All statistics was performed using Graph pad prism 4.0 (GraphPad Software Inc., La Jolla, CA). A p-value <0.05 was considered significant.

Results

Patient characteristics

Detailed patient characteristics are provided in Table 1. 24 patients were ultimately diagnosed with RAS. At the end of the study period, 5 patients were alive and did not undergo re-transplantation, 10 patients underwent re-transplantation and 9 patients died. Mean time of developing CLAD after transplantation was 1194±206 days. Mean time of follow-up after diagnosis of CLAD was 584±111 days (182-3521 days). 50% graft loss after CLAD diagnosis was 501 days. At diagnosis of CLAD, 6 patients fulfilled criteria for BOS but later on progressed to RAS, while 18 were immediately diagnosed with RAS. Most frequent complaints at diagnosis of CLAD were dyspnea (11/24, 45.8%), sputum (5/24, 20.8%) and cough (4/24, 16.7%). At the moment of the last CT, almost all patients suffered from dyspnea (23/24, 95.8%), while complaints of cough (10/24, 41.7%) and sputum production (8/24, 33.3%) were also frequently present.

CT findings at the diagnosis of CLAD

23 pre-CLAD CTs were available and compared with CLAD CT scans. The pre-CLAD CT was acquired 210±22 days before diagnosis of CLAD. Twelve of 23 pre-CLAD CT scans did not show any

abnormalities based on all evaluated parameters. In the 11 remaining pre-CLAD CT scans, the most frequent finding was peripheral consolidation (11/23, 47.8% of patients) (Table 2). Survival of the 11 patients with abnormalities on pre-CLAD CT was not significantly different compared to survival of the other 12 patients without abnormalities (p=0.49). Representative pre-CLAD CT scans from a patient with and without abnormalities and their progression is shown in figure 1 and 2 respectively. The CLAD-CT scans of 18/24 patients showed abnormalities. The severity of peripheral consolidation (p=0.064, 50.0% of patients), central ground glass (p=0.020, 33.3% of patients), peripheral ground glass (p=0.052, 50.0% of patients) and septal and non septal lines (p=0.020, 41.7% of patients) increased significantly from the pre-CLAD to CLAD CT. The number of patients showing an apicobasal gradient doubled from 3/24 patients to 6/24. There was no survival difference between patients with abnormalities at the moment of diagnosis of CLAD and those patients with a normal CT (p=0.16). As per definition, all spirometric data differed significantly at diagnosis of CLAD. FEV_1, FVC and FEV_1/FVC ratio significantly decreased (p<0.0001, p=0.002 and p=0.012) respectively. Survival after diagnosis of CLAD significantly correlated with absolute FVC (R=0.46 and p=0.021), FEV_1/FVC ratio (R=-0.55 and p=0.0050) at diagnosis of CLAD and tended to correlate with the presence of central consolidation (R=0.38 and p=0.061). No other associations were seen between findings on CT at the time of CLAD diagnosis and survival. More details are displayed in table 2 and 3.

Correlation between decline in pulmonary function and CT from pre CLAD to CLAD

From pre-CLAD to CLAD, there was a significant correlation between the absolute FEV_1-decrease and increase in bronchiectasis (R=-0.44 p=0.038) central ground glass (R=-0.43, p=0.047), peripheral ground glass (R=-0.43, p=0.047), architectural distortion (R=-0.42, p=0.049), volume loss (R=-0.42, p=0.049), and subpleural thickening (R=-0.63, p=0.0015). FVC decrease correlated significantly with bronchiectasis (R=-0.59; p=0.0038, peripheral consolidation (R=-0.48, p=0.025), central and

peripheral consolidation (R=-0.57, p=0.0052 and R=-0.61, p=0.0027) and pleural thickening (R=-0.54, p=0.0098). More details are shown in table 2 and 4.

CT findings after the diagnosis of CLAD

After CLAD was diagnosed, almost all parameters evolved over time. Between 3 to 6 months (mean 163±20days) after diagnosis of CLAD, CT scans of 3 patients still failed to show any alterations (compared to CT of 6 patients at diagnosis) suggesting that these patients remained in BOS (also evidenced by the absence of restriction of sprirometry) and only later evolved to RAS. Remarkably, some patients showed improvement rather than deterioration on CT, although FEV_1 further declined in all patients. A representative case is shown in figure 3. The last available CT scan (mean 443±87 days after diagnosis) showed alterations in every patient compared to the CT at CLAD diagnosis. Most prominent CT features at that time were bronchiectasis (79.2% of patients), peripheral consolidation (95.8%), peripheral ground glass (66.7%), architectural distortion (75.0%) and volume loss (62.5%). Comparing CT scoring from CLAD-CT, post-CLAD CT and last CLAD CT, demonstrated a significant increase in bronchiectasis (from 11.4 to 38.9%, p=0.0001), peripheral consolidation (13.1 to 38.3%, p=0.012), central (from 13.0 to 20.0%, p=0.0057) and peripheral (from 20.8 to 31.9%, p=0.0082) ground glass, architectural deformation (4.2 to 20.3%, p=0.0002), volume loss (4.2 to 15.0%, p=0.0094) and hilus retraction (0.3 to 2.5%, p=0.0302). The number of patients with an apicobasal gradient increased from 6 to 9. Figure 4 illustrates a patient with evolution towards upper lobe fibrosis. FEV_1 and FVC significantly decreased over time (p<0.0001 and p=0.0001 respectively). The FEV_1/FVC ratio remained comparable from CLAD till last post CLAD CT scan. More details about the different scores are shown in table 3 and 4.

Correlation between CT evolution and pulmonary function *after* diagnosis of CLAD

When correlating the changes in CT and the changes in pulmonary function from the moment of CLAD diagnosis until the last available post CLAD CT, significant correlations were found between the absolute FEV_1 decline and central ground glass (R=0.57, P=0.0099), peripheral ground glass (R=0.67, p=0.0016), architectural distortion (R=-0.49, p=0.031) and a trend towards a significant correlation with bronchiectasis (R=-0.42, p=0.072) was seen. The absolute decline in FVC correlated significantly with bronchiectasis (R=-0.50, p=0.027), central ground glass (R=0.48, p=0.042), peripheral ground glass (R=0.48, p=0.039) and architectural distortion (R=-0.51, p=0.026) and a trend towards a significant correlation with hilus retraction (R=-0.43, p=0.069) was seen. Full details are shown in table 3. There were no correlations between alterations in CT and survival after CLAD diagnosis.

Discussion

In 24 patients who ultimately fulfilled the RAS criteria, we evaluated changes in CT patterns from the pre-CLAD to end-stage CLAD stadium in relation to pulmonary function and survival. The most prominent features at diagnosis of CLAD compared to the last pre-CLAD CT were appearance of central and peripheral ground glass and septal and non septal lines. Survival after diagnosis of CLAD was only associated with FVC at the moment of CLAD diagnosis, but not with any CT alterations. When comparing the evolution of CT findings after diagnosis of CLAD, there are significant increases in (traction) bronchiectasis, central and peripheral consolidation, architectural deformation, volume loss and hilus retraction. The FVC and FEV_1 decrease correlated with CT alterations more specifically bronchiectasis, architectural deformation, central and peripheral ground glass.

To our knowledge, only the Toronto group so far reported CT findings in RAS patients. They compared the last CT scan taken during follow-up of RAS patients (only the last CT-scan) to BOS and stable patients. End-stage RAS was characterized by significant changes in interstitial opacities, traction bronchiectasis, architectural distortion and ground glass opacities. These observations are very similar to the evolution that we observe in our RAS patients, although many more patients in

our study showed (traction) bronchiectasis. Central and peripheral ground glass, central and peripheral consolidation (with 95.8% of patients showing peripheral consolidation in their last CT scan), architectural distortion, volume loss, hilus retraction, septal and non-septal lines, airtrapping and subpleural thicking were prominent features of RAS CT scans. As shown in figure 4, some patients show total fibrosis of the upper lobes with a relative sparing of the lower lobes. In our experience, this is associated with end-stage RAS, in fact an increasing number of patients (9/24, 37.5%) ultimately developed apical predominant fibrotic lesions, which is very comparable to the 40% as described by Sato and upper lobe fibrosis after lung transplantation has been published previously by others as well (10).

The added value of our study is that we compared the evolution within the same patients from pre-CLAD to end-stage RAS. As such, we could see that in the early disease stage, 6/24 (25%) developed at first an obstructive spirometric defect without any CT abnormalities and were, hence, diagnosed with BOS. At initial diagnosis of CLAD, CT scans were characterized by an increase in central and peripheral ground glass, which correlate with the decrease in FVC. Later on, there is no significant increase in the % of central and peripheral ground glass, but rather an increase in bronchiectasis, architectural deformation, volume loss, peripheral consolidation and hilus retraction. However, of all these different CT patterns, only bronchiectasis and central and peripheral ground glass correlated significantly with the FVC evolution.

As shown in figure 3 ground glass opacities seemed to resolve after an initial acute phase. This can be a response to treatment as the ground glass can be a manifestation of underlying infection or acute rejection. At the moment of CLAD this patient for example was treated with intravenous steroid pulse followed with oral tapered dose, but also with meropenem, tobramycine en ceftazidim which might explain the resolution of the ground glass. Nevertheless, the patient developed a restrictive pulmonary function defect, which persisted throughout time.

FVC at diagnosis of CLAD correlated with post-CLAD survival. This indicates that patients with an initial high FVC have a better survival after CLAD diagnosis; these are indeed the patients who were initially diagnosed with BOS and only later on evolved to RAS and as already described previously, BOS patients have a better survival compared to RAS patients (5,6). From our current results, it seems that the FVC decrease appears to be more predictive towards survival than specific changes on the CT. This is comparable to interstitial pulmonary fibrosis (IPF), where most studies use FVC evolution as an endpoint and not CT evolution (11). However, some patients are often too sick to perform pulmonary function tests, which makes it more difficult to link evolutionary changes in CT and spirometry, especially in the later stages of the disease (12). Sato et al. recently described a stepwise pattern of decline in pulmonary function towards RAS and noted ARDS-like early exacerbation with mainly ground glass on CT, which resolved but evolved in consolidation, reticular patterns and bronchiectasis (13). However they used mainly CT data during exacerbations and not at routine time points, whereas we report the CT evolution patterns, to be able to correlate CT changes with important clinical variables like spirometry and survival. We agree that some patients indeed start from an acute event (exacerbation), but 11 of our later RAS patients already showed presence of abnormalities on CT before the FEV_1 decreased, which suggests that some early manifestations of RAS may be present which is not detected on pulmonary function and which is not characterized by an apparent exacerbation.

In comparison with a previous study where radiological alterations in azithromycin responsive (neutrophilic CLAD) versus azithromycin non-responsive patients (mostly obstructive patients) were assessed, the biggest difference with the non-responders in that previous study and our current study is the small degree of air trapping in the RAS patients, which is in agreement with the previously reported results of the Toronto group (5). This indicates that air trapping is more specific for the BOS phenotype and occurs less frequently in the RAS patients. In patients who do have air trapping this may probably be a manifestation of the previous BOS diagnosis with underlying OB lesions being present.

This study has limitations as we have a high rate of re-transplantation within our RAS cohort, which might explain why we could not detect a correlation between CT changes and graft loss after diagnosis. Indeed, given the poor outcome of RAS, we have chosen to early retransplant these patients, at least when they qualify for it. Moreover the evolution of only 24 patients was described. This is, however, our entire RAS cohort. We started our study from the moment of CLAD diagnosis and not at the moment of RAS. This is because we lack sufficient TLC values to adequately judge the exact moment of diagnosing RAS. Therefore, we opted to start from the known fact that the FEV_1 decreased, which led to the initial diagnosis of CLAD. Doing so, we have an objective criteria for comparing findings in the pre-CLAD, CLAD- post-CLAD and late CLAD stadium.

In conclusion, this study shows that in the early stages of RAS central and peripheral ground glass are the most prominent features on CT, while in the later stages bronchiectasis, traction, central and peripheral consolidation, architectural deformation, volume loss and hilus retraction are more observed. CT alteration are helpful to diagnose RAS but do not seem to be able to predict survival.

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Table 1: Patient characteristics of the 24 patients who developed Chronic Lung Allograft Dysfunction and ultimately fulfilled the criteria of the RAS phenotype

Age at transplant, years	36.8±3.5
Underlying disease, n	
Emphysema	9
Cystic fibrosis	5
Pulmonary fibrosis	4
Pulmonary hypertension	2
Other	4
Male/Female, n	13/11
Double lung/Heart-Lung transplantation, n	22/2
Alive/Re-transplant/death	5//10//9
Time of CLAD diagnosis, post transplant days	1194±206

Table 2: Prevalence of CT findings before, at and after the diagnosis of Chronic Lung Allograft Dysfunction

	Pre-CLAD	CLAD	Post CLAD	Last CLAD
Bronchiectasis, n(%)	3 (13.0%)	7 (29.1%)	12 (52.2%)	19 (79.2%)
Mucus, n(%)	3 (13.0%)	5 (20.8%)	2 (8.7%)	2 (8.3%)
Nodules, n(%)	4 (17.4%)	6 (25.0%)	5 (21.7%)	3 (12.5%)
Airway wall thickening, n(%)	1 (4.3%)	1 (4.2%)	2 (8.7%)	3 (12.5%)
Consolidation central, n(%)	2 (8.7%)	4 (16.7%)	7 (30.4%)	12 (50%)
Consolidation peripheral, n(%)	10 (43.5%)	12 (50.0%)	14 (60.9%)	23 (95.8%)
Ground glass central, n(%)	1 (4.3%)	8 (33.3%)	10 (43.5%)	12 (50%)
Ground glass peripheral, n(%)	5 (21.7%)	12 (50%)	14 (60.9%)	16 (66.7%)
Architectural distortion, n(%)	3 (13.0%)	5 (20.8%)	11 (47.8%)	18 (75.0%)
Volume loss, n(%)	3 (13.0%)	5 (20.8%)	9 (39.1%)	15 (62.5%)
Hilus retraction, n(%)	1 (4.3%)	1 (4.2%)	3 (13.0%)	8 (33.3)
Septal and non-septal lines, n(%)	3 (13.0%)	10 (41.7%)	9 (39.1%)	12 (50.0%)
Thickening axial interstitium, n(%)	0 (0.0%)	2 (8.3%)	2 (8.7%)	3 (12.5%)
(Sub)pleural thickening, n(%)	4 (17.3%)	8 (33.3%)	8 (34.8%)	9 (37.5%)
Airtrapping, n(%)	4 (17.3%)	6 (25%)	5 (21.7%)	8 (33.3%)
Apicobasal gradient, n(%)	3 (13.0%)	6 (25%)	7 (30.4%)	9 (37.5%)

Table 3: Computed tomographic and spirometric evolution towards the diagnosis of CLAD

	CT findings			Correlation with FEV_1		Correlation with FVC	
	Pre- CLAD*	CLAD	P	R	**P**	R	**P**
Bronchiectasis	7.2±4.5	11.4 ±4.5	0.22	-0.44	0.038	-0.59	**0.0038**
Mucus	1.7±1.2	5.0 ±3.0	0.88	-0.37	0.086	-0.26	0.24
Nodules	5.5±2.4	8.0±3.4	0.82	-0.20	0.37	-0.22	0.32
Airway wall thickening	0.6±0.6	0.6 ±0.6	1.00	-0.31	0.16	-0.26	0.25
Consolidation central	1.2±0.9	3.9 ±2.2	0.19	-0.07	0.74	-0.10	0.67
Consolidation peripheral	7.5±2.9	16.1 ±4.4	0.064	-0.40	0.063	-0.48	**0.025**
Ground glass central	0.9±0.9	13.0 ±4.5	**0.020**	-0.43	**0.047**	-0.57	**0.0052**
Ground glass peripheral	5.8±3.1	20.8 ±6.1	**0.052**	-0.43	**0.047**	-0.61	**0.0027**
Architectural deformation	2.6±1.6	4.2 ±2.2	0.32	-0.42	**0.049**	-0.39	0.07
Volume loss	2.6±1.6	4.2 ±2.2	0.32	-0.42	**0.049**	-0.39	0.07
Hilus retraction	0.3±0.3	0.3±0.3	1.00	0.08	0.70	-0.03	0.88
Septal and non-septal lines	2.3±1.5	17.5±5.6	**0.020**	-0.19	0.39	-0.26	0.24
Thickening axial interstitium	0.0±0.0	1.9±1.5	0.50	-0.10	0.66	-0.02	0.94
Pleural thickening	2.3±1.0	5.6±2.0	0.22	-0.63	**0.0015**	-0.54	**0.0098**
Airtrapping	2.9±1.6	6.9±3.3	0.63	-0.23	0.29	-0.18	0.41
Apicobasal gradient	3	6					
FEV_1 (L)	2.75±0.17	1.96±0.14	**<0.0001**				
FVC (L)	3.53±0.22	2.82±0.21	**0.0005**				
FEV_1/FVC ratio	79.34±2.3	72.04±3.08	**0.012**				

*Time before CLAD was 210±22 days. P-value represents the result of the Wilcoxon matched pair test. Correlation analysis with the FVC and FEV_1 decline was performed using a Spearman rank test using the scores of the pre-CLAD CT-last CT. Significant p-values are presented in bold. CLAD=Chronic Lung Allograft Dysfunction. FEV_1=Forced Expiratory Volume in the first second. FVC=Forced Vital Capacity.

Table 4: Computed tomographic and spirometric evolution after the diagnosis of CLAD

	CT finding				**Correlation FEV_1**		**Correlation FVC**	
	CLAD	Post CLAD	Last CLAD	p	R	p	R	p
Bronchiectasis	11.4 ±4.5	22.0±5.8	38.9±6.5	**0.0001**	-0.42	**0.072**	-0.50	**0.027**
Mucus	5.0 ±3.0	0.6±0.4	0.6±0.4	0.25	0.27	0.26	-0.05	0.84
Nodules	8.0±3.4	5.2±2.4	3.1±1.9	0.080	0.31	0.19	0.06	0.75
Airway wall thickening	0.6 ±0.6	0.9±0.6	1.7±0.9	0.27	0.043	0.86	0.25	0.29
Consolidation central	3.9 ±2.2	8.1±2.9	11.1±3.3	0.080	-0.25	0.29	0.00	1.00
Consolidation peripheral	16.1 ±4.4	20.0±5.2	38.3±5.1	**0.012**	-0.062	0.80	-0.17	0.48
Ground glass central	13.0 ±4.5	19.7±6.1	20.0±6.0	**0.0057**	0.57	**0.0099**	0.48	**0.042**
Ground glass peripheral	20.8 ±6.1	30.4±6.5	31.9±6.7	**0.0082**	0.67	**0.0016**	0.48	**0.039**
Architectural deformation	4.2 ±2.2	12.4±3.7	20.3±4.4	**0.0002**	-0.49	**0.031**	-0.51	**0.026**
Volume loss	4.2 ±2.2	9.3±3.0	15.0±3.7	**0.0009**	-0.10	0.67	-0.28	0.25
Hilus retraction	0.3±0.3	0.9±0.5	2.5±0.8	**0.0302**	-0.15	0.53	-0.43	**0.069**
Septal and non-septal lines	17.5±5.6	12.5±4.0	16.1±4.2	0.38	0.20	0.41	0.050	0.84
Thickening axial interstitium	1.9±1.5	2.0±1.5	3.3±1.9	0.37	0.00	1.00	0.00	1.00
Pleural thickening	5.6±2.0	7.5±2.5	10.3±3.3	0.062	0.21	0.39	0.0085	0.98
Airtrapping	6.9±3.3	8.4±4.0	10.2±3.3	0.66	-0.27	0.27	0.0005	0.98
Apicobasal gradient	6	7	9					
FEV_1	1.96±0.14	1.72±0.16	1.26±0.11					
FVC	2.82±0.21	2.66±0.27	1.90±0.17					
FEV_1/FVC	72.04±3.08	68.0±4.0	69.6±3.9					

The displayed p-value shows the results of the Friedman rank test. Correlation with the absolute FEV1 and FVC decline was performed with the Spearman rank test using the scores of the last CLAD CT-CLAD CT. Significant p-values are presented in bold. CLAD=Chronic Lung Allograft Dysfunction. FEV_1=Forced Expiratory Volume in the first second. FVC=Forced Vital Capacity.

Figure legend

Figure 1:

A 55 year old, female patient with abnormalities on sagittal computed tomography (CT) reconstruction of the right lung before Chronic Lung Allograft Dysfunction (CLAD) diagnosis. CLAD was diagnosed 1316 days after double lung transplantation for sarcoidosis. The left panel shows the CT before development of CLAD with peripheral consolidation and peripheral ground glass being present. There is not much evolution visible on the next CT at CLAD diagnosis 43 days later. The last CT 441 days later shows a typical Restrictive Allograft Syndrome pattern with extensive peripheral ground glass, architectural distortion and traction bronchiectasis being present.

Figure 2:

A 28 year old, male patient without abnormalities on the computed tomography (CT) exam before Chronic Lung Allograft Dysfunction (CLAD) diagnosis. CLAD was diagnosed 2623 days after double lung transplantation for primary pulmonary hypertension. Last CT shows ground glass, consolidation, volume loss, architectural distortion, hilus retraction and traction bronchiectasis as signs of fibrosis in the upper lobe of the right lung.

Figure 3:

A 29 year old, female patient who at initial Chronic Lung Allograft Dysfunction (CLAD) diagnosis had a decrease in FEV_1 and Total Lung Capacity (Restrictive Allograft Syndrome diagnosis), with concomitant peripheral and central ground glass and thickening of intra- and interlobular septa, which largely resolved on the last available computed tomography (CT) exam with some

development of traction bronchiectasis 155 days after RAS diagnosis. RAS was diagnosed 3521 days after initial transplantation for cystic fibrosis.

Figure 4:

A 23 year old female patient, transplanted for cystic fibrosis, with an initial slightly abnormal pre-Chronic Lung Allograft Dysfunction (CLAD) computed tomography (CT) examination with limited ground glass in the lower lobes. At the time of CLAD, ground glass and especially septal lines were extensively present. On the two CT exams after CLAD, progressive upper lobe architectural distortion, volume loss, consolidation and traction bronchiectasis developed with hilar retraction consistent with upper lobe fibrosis. This is the patient with the longest evolution of restrictive allograft syndrome (RAS) in our cohort. Time between diagnosis of CLAD and last CT (right lower panel) is 1909 days.

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